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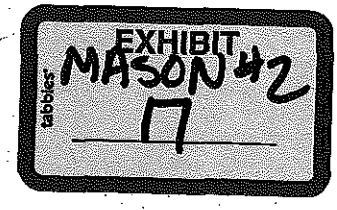

Interpretation of Excessive Serum Concentrations of Digoxin in Children

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Between January 1981 and April 1984, excessive serum concentrations of digoxin (5 ng/ml or higher) were recorded in 47 children, aged 2 days to 16 years. In 10 patients, the high concentrations were measured 9.25 to 48 hours after death and were significantly higher than antemortem levels in all cases (8.3 ± 2.4 (± standard deviation) postmortem vs 3.3 ± 1.5 antemortem, <0.0001). In 15 patients (40.5% of the living patients) serum concentrations of 5 ng/ml or higher reflected sampling errors; drug levels were monitored too closely to the administration of a dose. None of these children had toxic manifestations of digoxin. In 10 patients, the excessive concentrations were associated with renal failure and a prolonged elimination half-life ($T^1/_2$) of digoxin; in 3 of these patients, there were signs of digoxin toxicity. Six cases were caused by digoxin overdose (accidental ingestions, pharmacy error and a suicide attempt). In 6 additional cases, the existence of an endogenous digoxin-like substance (EDLS) was shown to contribute to the excessive levels of the drug. One case could be attributed to digoxin-amiodarone interaction. In 10 of 37 living patients, digoxin toxicity was diagnosed. After excluding the 15 sampling errors and 6 cases with EDLS, this represents 63% of the cases. There was a good correlation between digoxin elimination $T^1/_2$ and serum creatinine concentrations (r = 0.71, p <0.01). The above observations suggest that excessive serum concentrations of digoxin may not necessarily reflect potentially toxic levels. Sampling errors, postmortem determinations and circulating EDLS should be considered as explanations when toxic levels of digoxin are found.

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Digoxin is one of the most ancient drugs in contemporary medicine. However, despite 2 centuries of clinical use, its use remains controversial.[1,2] Because of its narrow margin of safety, digoxin serum concentrations must be repeatedly monitored during chronic treatment. In adults, the therapeutic range is 1 to 2.5 ng/ml. However, children are believed to be less sensitive to digoxin and need higher doses.[3,4] However, excessive serum concentrations of the cardiac glycoside should not automatically be interpreted as reflecting toxicity. In the present studies, we reviewed cases of excessive serum digoxin concentrations in children to identify the causes of these levels.

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Methods

To identify excessive serum determinations of digoxin, the Therapeutic Drug Monitoring Laboratory charts of digoxin at the Hospital for Sick Children in Toronto were screened for the period between January 1981 and April 30, 1984. All assays were performed by a radioimmunoassay (New England Nuclear until the end of March 1983 or TDX (Abbot, Ltd.) since April 1983). The coefficient of variation for the tests in this laboratory is less than 5% for levels above 1 ng/ml. An "excessive level" was arbitrarily defined as 5 ng/ml or higher, because in children, some investigators believe that toxicity occurs at levels higher than the adult range of 1 to 2.5 ng/ml.[4] A level of 5 ng/ml or greater, on the other hand, is not controversial in this respect. The charts of the children in whom serum concentrations were 5 ng/ml or higher were reviewed. Details of their ages, weights, diseases, renal function, digoxin and other drug therapy were obtained.

Digoxin toxicity was defined by clinical signs (anorexia, nausea, vomiting, bradycardia, arrhythmia and abdominal pain) and electrocardiographic signs. Digoxin elimination half-life was determined by least-squares linear regressions of the concentration-time data after stopping the drug, plotted on semilogarithmic paper. Serum digoxin concentrations determined in patients after they died compared with ante-

mortem levels by the Student *t* test for paired results in 10 children. The correlation between digoxin elimination T½ and creatinine serum concentration was assessed by least-squares linear regression.

Results

Between January 1981 and April 1984, serum digoxin concentrations of 5 ng/ml or higher were detected in 47 children. They were 2 days to 16 years old. Table I is a list of the various factors that contributed to the excessive levels. In some children, more than 1 factor could be implicated, and in 4 children the high levels of digoxin could not be explained by any of the putative mechanisms.

Postmortem serum concentrations of digoxin: In 10 infants, all of whom had inoperable congenital heart disease, postmortem levels were significantly higher (8.3 ± 2.4 ng/ml) than antemortem levels (3.3 ± 1.5 ng/ml) ($p < 0.0001$) (Fig. 1). The postmortem determinations were performed 9.25 to 48 hours after death. No correlation was found between the length of time elapsed until the postmortem determination and the rate of elevation in serum digoxin concentration.

Sampling error: In 15 instances, digoxin levels of 5 ng/ml or higher could be well explained by sampling blood 5 minutes to 3 hours after a dose (peak level). Subsequently, the dose was discontinued and repeated assessment failed to reveal excessive levels. None of these children had clinical signs of digoxin toxicity.

Case 1: A 4-month-old girl suffering from atrioventricular canal, cleft mitral valve and congestive heart failure was treated intravenously with digoxin in a dose of 4 μg/kg twice daily. She appeared to benefit from the drug and previous serum concentrations recorded before a dose were 1.5 to 2 ng/ml. One morning a level of 6.2 ng/ml was recorded, and digoxin therapy was stopped despite the potential benefit and lack of toxic signs. Twenty-four hours later, the digoxin level was 1.7 ng/ml. Investigation revealed that the excessive concentration was erroneously measured 20 minutes after the administration of her morning dose.

Overdose: Overdose could clearly be determined in 6 cases, 4 of which occurred outside the hospital. Two infants swallowed an undetermined number of digoxin tablets that belonged to family members. In 1 case, a child was given an excessive dose of Lanoxin® syrup because of a pharmacy labeling error. A 15-year-old girl consumed 32 tablets of her father's digoxin during a suicide attempt. Because of induced emesis and charcoal ingestion, it was impossible to determine how much of the drug was eventually absorbed.

Renal insufficiency: In 10 instances, renal insufficiency was evident at the time of the excessive serum concentration of digoxin. Three patients had end-stage kidney diseases; however, the digoxin dose was not reduced and dosing intervals were not prolonged to adjust for the renal disease. Acute digoxin toxicity occurred in 3 patients. In a few other cases, acute renal insufficiency was not considered in adjusting digoxin dosage.

Endogenous digoxin-like substance (EDLS): Six newborn babies and infants showed evidence of circulating EDLS, which could partially explain readings of

TABLE I Mechanisms Involved in Excessive (≥5 ng/ml) Serum Concentration of Digoxin in 47 Children

	No. of Children*
High postmortem levels	10
Sampling error	15
Overdose	6
Renal insufficiency	10
Endogenous digoxin like substance	6
Digoxin-amiodarone interaction	1

* In some children, more than 1 mechanism could be shown (e.g, renal failure and endogenous digoxin-like substances), whereas in 4 cases, the high measured level of digoxin could not be explained by any of the above factors.

excessive digoxin. All six were critically ill, and in 4 patients, there was associated acute renal failure (Table II). Because of high serum concentrations, digoxin therapy was stopped; however digoxin levels as measured by the routine radioimmunoassay continued to rise in 4 of them. In 2 other patients, after an initial decrease in serum concentrations, the digoxin level eventually "plateaued" despite cessation of therapy for a few days.

Case 2: A critically ill 5-week-old boy with severe aortic stenosis, cardiac failure and endocarditis was treated with digoxin, 10 μg/kg twice daily, and his measured serum concentration was 1.8 ng/ml. Two days later, during deterioration of his general condition, a predose level was 6 ng/ml, and consequently digoxin therapy was stopped. However, 2 days later, a few hours

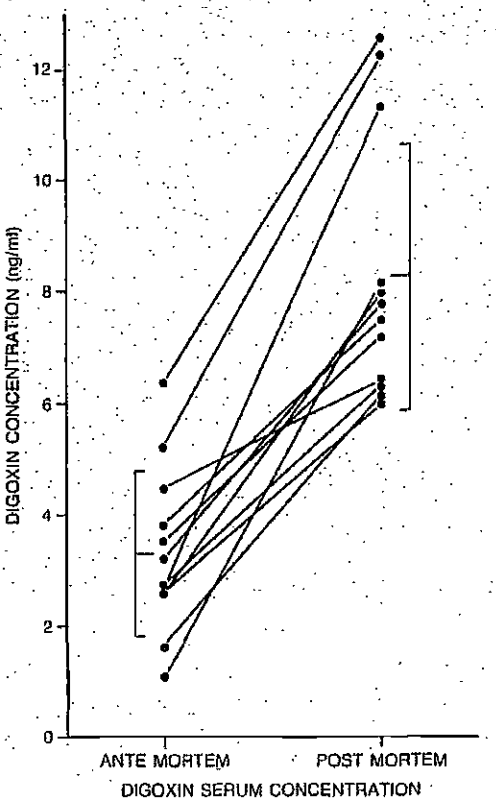

FIGURE 1. Postmortem concentrations of digoxin are significantly higher than antemortem concentrations ($p < 0.0001$).

TABLE II Characteristic of Six Infants Who Had Evidence That Endogenous Digoxin-Like Substances Contributed to Excessive Digoxin Readings

Pt	Wt (kg)	Age (days)	Diagnosis	Highest Serum Digoxin Reading (ng/ml)
A.L.	0.51	21	PDA, RDS	6.0
C.M.	3.2	37	RDS, aortic stenosis	11.4
C.L.	4.0	7	Septic shock, RI	6.6
C.Z.	5.2	60	Endocardial fibroelastosis, RI	5.2
E.C.	3.8	20	Multiple thrombi, RI	7.2
S.C.	5.5	270	AV canal, RI, Down's syndrome	6.2

AV = atrioventricular; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; RI = renal insufficiency; SBE = subacute bacterial endocarditis.

before his death, the serum digoxin concentration was 11.4 ng/ml.

Case 3: A 9-month-old boy with Down's syndrome and atrioventricular canal was referred from another hospital because of deep coma secondary to an erroneous overdose of morphine. On admission, a serum digoxin concentration of 6.2 ng/ml was found, and digoxin therapy was discontinued. During the following days, the serum digoxin concentration slowly decreased (with a $T^1/_2$ of 64 hours), corresponding to transient renal failure. However, after reaching a level of 1.3 ng/ml, serum digoxin concentration stayed unchanged at levels between 1.3 and 1.5 ng/ml for an additional week, although digoxin was not administered.

Interaction of digoxin with other drugs: A case of amiodarone-associated digoxin toxicity has been reported elsewhere.[5] Digoxin-quinidine interaction has been reported in a group of children and may cause toxic signs[6]; however, none of the patients in these studies had a level of 5 ng/ml or higher. Similarly, in a group of newborn infants with patent ductus arteriosus, serum digoxin concentrations were acutely elevated after administration of indomethacin, although digoxin levels did not reach 5 ng/ml.[7]

Digoxin toxicity: Ten patients had evidence of digoxin toxicity (Table III). Nine of these patients had digoxin overdose or renal insufficiency. In some of the more critically ill children, digoxin toxicity may have been masked by their generalized disease. In none of the cases of high digoxin concentrations resulting from erroneous sampling were there signs of digoxin toxicity. After excluding these 15 cases and an additional 6 cases of EDLS, digoxin toxicity could be diagnosed clinically in 63% of cases with serum digoxin concentrations of 5 ng/ml or higher.

Digoxin elimination half-life: In 19 cases, there were sufficient data to calculate the correlation between serum creatinine concentration and digoxin elimination $T^1/_2$ ($r = 0.71$, $p < 0.01$) (Fig. 2). One child had a digoxin-amiodarone interaction; despite relatively adequate renal function there was a prolonged $T^1/_2$ of digoxin, presumably because of inhibition of the renal tubular secretion of digoxin without affecting glomerular filtration rate.[5]

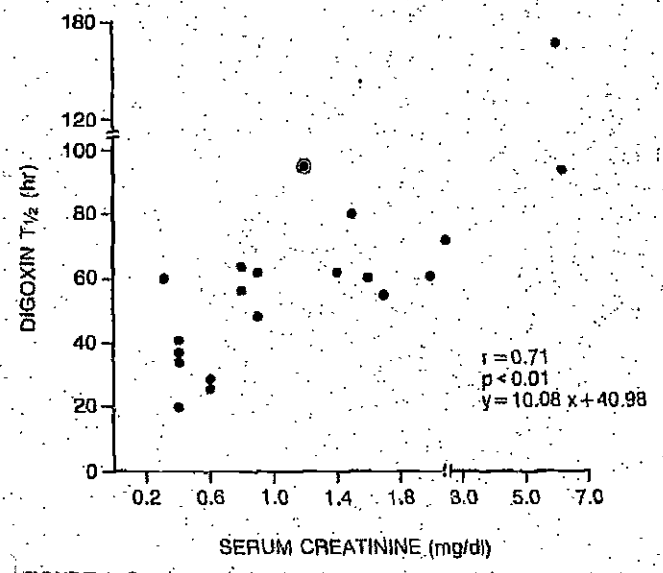

FIGURE 2. Good correlation between serum creatinine concentration and digoxin elimination half-life ($T^1/_2$). The circled point represents a child with digoxin-amiodarone interaction; despite relatively adequate renal function there was a prolonged $T^1/_2$.

Discussion

The arbitrary cutoff value of 5 ng/ml that we chose does not imply that digoxin toxicity cannot occur at lower levels.[8] Halkin et al[9] found electrocardiographic toxic signs in 4 out of 11 neonates and infants who had digoxin levels higher than 2 ng/ml. Lanese and Mizkin,[10] on the other hand, found no relation between serum concentrations and onset or persistence of cardiac arrhythmias.[10] However, in our attempt to interpret excessive digoxin levels, we had to choose a level that is identified by all clinicians as potentially toxic. Several mechanisms could be positively identified as causing or contributing to excessive serum concentrations of the cardiac glycoside. Postmortem levels were significantly higher than antemortem levels in all children studied (Fig. 1). These results are consistent with previous reports,[11,12] suggesting that after death, redistribution of digoxin takes place. We recently reproduced these results in rats, showing that after death, digoxin reenters the blood from various tissue compartments, presumably because of cessation of the active accumulation of the glycoside that occurs during life.[13] These observations may have important medicolegal implications. An attempt to prove digoxin intoxication as a cause of death

may be hampered by the fact that postmortem levels may be 1.5 to 10 times higher than antemortem levels. Consequently, one cannot readily use these postmortem data to predict antemortem concentrations. Only if postmortem concentrations are in the therapeutic range can one assume that antemortem concentrations were not excessive.

The high incidence of sampling errors (43% of living cases) was surprising. In all these cases a digoxin level of 5 ng/ml or higher was interpreted as potentially toxic, and the drug was discontinued for varying lengths of time. After intravenous, intramuscular or oral administration of digoxin, large amounts of the drug circulate in the blood. The distribution of digoxin is relatively slow, and eventually only about 1% of the dose stays in the blood, the rest being distributed into muscle, liver, kidney and skin.[12] Consequently, a post-dose sampling may yield extremely high levels, which do not correlate with or reflect toxicity. In none of these cases were there signs of digoxin toxicity.

Digoxin overdose appeared to be the single most common cause of digoxin toxicity, accounting for 60% of the cases of verified toxicity in the present study (Table III). Children with normal hearts who were exposed to the drug could tolerate serum concentrations of 15 ng/ml relatively well, and did not have signs of toxicity when levels decreased to 6 ng/ml. On the other hand, children with compromised hearts showed signs of toxicity when levels reached 5 to 6 ng/ml. Other factors, including hypoxia, hypokalemia, hypercalcemia, hypomagnesemia, acid-base disturbances and administration of sympathomimetic amines, may precipitate digoxin intoxication.[8] Toxic symptoms such as visual disturbances and malaise reported in adults are difficult to judge in young children.[8] Nausea and persistent vomiting, on the other hand, are frequent manifestations in children. These characteristics are reflected in our patients (Table III). Similar to previous reports in children, most of our patients with signs of toxicity had atrial arrhythmias.[8]

In humans, digoxin is eliminated almost entirely unchanged by the kidney through both glomerular filtration and tubular secretion.[13] This association is clearly documented by the correlation between the elimination $T^1/_2$ of digoxin and creatinine serum concentration. Several exceptions must be taken into account: Several drugs, including the antiarrhythmic agents quinidine, verapamil and amiodarone decrease renal clearance of digoxin without affecting glomerular filtration rate[6]; consequently, they may cause accumulation and toxicity of digoxin. In such cases, prolongation of digoxin $T^1/_2$ will not be accompanied by an increase in serum creatinine concentration. This is exemplified in the present study by the child who had digoxin toxicity associated with amiodarone (Fig. 2, circled point). Whenever one of these drugs is coadministered with digoxin, a careful assessment of digoxin serum concentration should be carried out with appropriate reduction of the dose to avoid toxicity.

During renal failure, both clearance and volume of distribution of digoxin are decreased, and therefore the loading and maintenance dose should be significantly reduced and the dosing interval prolonged.

TABLE III Clinical and Electrocardiographic Manifestations of Digoxin Toxicity in 10 Children

	No. of Pts
Mechanisms of accumulation	
Overdose	6
Renal insufficiency	3
Digoxin-amiodarone interaction	1
Clinical signs	
Anorexia	4
Nausea	4
Vomiting	4
Lethargy	3
Congestive heart failure	2
Electrocardiographic signs	
Sinus bradycardia	3
Atrial escape beats	1
Cardiac arrest	2
Changes in ST segment	2
Wenckebach phenomenon	1
1st-degree atrioventricular block	3
Nodal rhythm	1
Bigeminy	1
Idioventricular rhythm	1

The possible existence of EDLS in 6 of our patients is of particular interest. Previous studies show that EDLS exists in the blood of a majority of preterm infants[14–16]; however, none of the infants in these studies was receiving digoxin. Unexplained elevation of digoxin levels in critically ill adults with renal failure has been attributed to EDLS.[17] Our children with EDLS continued to have increasing digoxin levels long after discontinuation of cardiac glycoside therapy without evidence of digoxin toxicity. In other cases, digoxin serum concentrations decreased to a "plateau" level that was maintained for long periods. These phenomena might have been partially explained by acute changes in distribution volume and clearance; however, even in renal failure digoxin levels decrease gradually and do not increase.[18] Moreover, these possible changes cannot explain the residual steady readings of digoxin long after stopping treatment. Until an assay is available that can differentiate between digoxin and EDLS, it is advisable to measure a pretreatment level of digoxin in newborn infants or critically ill children. This may yield some information on EDLS levels; however, these levels are not stable over time, and a simple subtraction of pretreatment EDLS level from apparent reading of digoxin during treatment may not yield the "true" level of digoxin.

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